LEXSEE 225 F3D 1349

SIBIA NEUROSCIENCES, INC., Plaintiff-Appellee, v. CADUS PHARMACEUTICAL CORPORATION, Defendant-Appellant.

99-1381

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

225 F.3d 1349; 2000 U.S. App. LEXIS 22516; 55 U.S.P.Q.2D (BNA) 1927

September 6, 2000, Decided

PRIOR HISTORY: [**1] Appealed from: United States District Court for the Southern District of California. Judge Irma E. Gonzales.

DISPOSITION: REVERSED.

CASE SUMMARY:

PROCEDURAL POSTURE: Defendant appealed the judgment of the United States District Court for the Southern District of California entered in plaintiff's favor after a jury found that the patent claims at issue concerning a cell-based screening method were infringed and were not invalid.

OVERVIEW: Plaintiff owned a patent which was directed to a cell-based screening method useful for the identification of compounds that exhibited agonist and antagonist activity with respect to particular cell surface proteins. According to the patent, the claimed methods were particularly effective because they allowed a scientist to rapidly and reliably screen large numbers of compounds for agonist and antagonist activity. Plaintiff sued defendant for patent infringement. Defendant argued that the claims of the patent were invalid as obvious under *35 U.S.C.S. § 103*(a) or as not enabled under *35 U.S.C.S. § 112*. A jury rejected defendant's invalidity defenses of obviousness and non-enablement. The court held that a patent claim was invalid if the differences between the subject matter sought to be patented and the prior art were such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. The court reversed judgment, holding that the asserted claims were obvious as a matter of law because plaintiff based its patent on a prior art reference and there was evident motivation to modify the prior art reference.

OUTCOME: Judgment reversed; defendant did not infringe plaintiff's patent because the patent's claims were obvious as a matter of law since the patent was based on a prior art reference and there was evident motivation for plaintiff to modify the prior art reference.

LexisNexis(R) Headnotes

Civil Procedure > Appeals > Standards of Review > Substantial Evidence
Civil Procedure > Appeals > Standards of Review > De Novo Review
[HN1] An appellate court reviews the denial of a motion for judgment as a matter of law following a jury verdict by reapplying the district court's standard of review. Thus, an appellate court reviews issues of law de novo. With regard to factual findings, an appellate court must presume that the jury resolved all factual disputes in favor of the prevailing party, and the appellate court must leave those findings undisturbed as long as they are supported by substantial evidence.

Civil Procedure > Appeals > Standards of Review > Substantial Evidence
[HN2] A factual finding is supported by substantial evidence if a reasonable jury could have found in favor of the prevailing party in light of the evidence presented at trial. Substantial evidence is more than a mere scintilla. It means such relevant evidence as a reasonable mind might accept as adequate to support a conclusion. Thus, substantial evidence review involves an examination of the record as a whole, taking into consideration evidence that both justifies and detracts from the decision of the fact-finder.

Civil Procedure > Trials > Judgment as Matter of Law
Civil Procedure > Appeals > Standards of Review
[HN3] In reviewing the record on a denial of a motion for judgment as a matter of law, an appellate court must draw all reasonable inferences in favor of the prevailing party, and not make credibility determinations or substitute its view of the conflicting evidence for that of the

jury. If, however, after reviewing all of the evidence in a light most favorable to the prevailing party, the court is convinced that a reasonable jury could not have found in that party's favor, the court must reverse the denial of judgment as a matter of law.

Patent Law > Infringement Actions > Defenses > Patent Invalidity > Fact & Law Issues
Patent Law > Jurisdiction & Review > Standards of Review > De Novo Review
[HN4] In patent law, the first step in any invalidity analysis is claim construction, an issue of law that an appellate court reviews de novo.

Patent Law > Nonobviousness > Elements & Tests > Ordinary Skill Standard
Patent Law > Nonobviousness > Elements & Tests > Prior Art
Patent Law > Nonobviousness > Elements & Tests > Claimed Invention as a Whole
[HN5] A patent claim is invalid if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *35 U.S.C.S. § 103*(a).

Patent Law > Nonobviousness > Evidence & Procedure > Fact & Law Issues
Patent Law > Claims & Specifications > Enablement Requirement > General Overview
Patent Law > Nonobviousness > Elements & Tests > General Overview
[HN6] While the ultimate conclusion of obviousness is for the court to decide as a matter of law, several factual inquiries underlie this determination. These inquiries include the scope and content of the prior art, the level of ordinary skill in the field of the invention, the differences between the claimed invention and the prior art, and any objective evidence of non-obviousness such as long-felt need, and commercial success.

Patent Law > Inequitable Conduct > Effect, Materiality & Scienter > General Overview
Patent Law > Infringement Actions > Defenses > Patent Invalidity > Validity Presumption
Patent Law > Nonobviousness > Evidence & Procedure > Presumptions & Proof
[HN7] Because an issued patent is presumed valid, there must be clear and convincing evidence supporting the obviousness determination.

Patent Law > Nonobviousness > Elements & Tests > Prior Art
Patent Law > Nonobviousness > Elements & Tests > Ordinary Skill Standard
Patent Law > Inequitable Conduct > Effect, Materiality & Scienter > General Overview
[HN8] In appropriate circumstances, a single prior art reference can render a claim obvious. However, there must be a showing of a suggestion or motivation to modify the teachings of that reference to the claimed invention in order to support the obviousness conclusion. This suggestion or motivation may be derived from the prior art reference itself, from the knowledge of one of ordinary skill in the art, or from the nature of the problem to be solved.

Patent Law > Nonobviousness > Evidence & Procedure > Fact & Law Issues
Patent Law > Nonobviousness > Elements & Tests > Prior Art
Patent Law > Inequitable Conduct > Effect, Materiality & Scienter > General Overview
[HN9] In patent law, determining whether there is a suggestion or motivation to modify a prior art reference is one aspect of determining the scope and content of the prior art, a fact question subsidiary to the ultimate conclusion of obviousness

Patent Law > Nonobviousness > Elements & Tests > Prior Art
Patent Law > Nonobviousness > Elements & Tests > Ordinary Skill Standard
Patent Law > Nonobviousness > Elements & Tests > Secondary Considerations
[HN10] In patent law, when the record establishes a strong case of obviousness based on the teachings of the prior art, the fact that the product was successful does not overcome the conclusion of obviousness.

Patent Law > Infringement Actions > Burdens of Proof
[HN11] In patent law, for objective evidence to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention.

Patent Law > Claims & Specifications > Claim Language > Dependent Claims
Patent Law > Claims & Specifications > Claim Language > Representative Claims
Patent Law > Nonobviousness > Evidence & Procedure > Fact & Law Issues
[HN12] In patent law, dependent claims fall with the independent claim on which they depend unless argued separately.

COUNSEL: Stephen P. Swinton, Cooley Godward LLP, of San Diego, California, argued for plaintiff-appellee. With him on the brief were Anthony M. Stiegler, J. Christopher Jaczko, Kent M. Walker, and Amy S.

Hellenkamp.

Laura A. Coruzzi, Pennie & Edmonds LLP, of New York, New York, argued for defendant-appellant. With her on the brief was S. Leslie Misrock. Of counsel on the brief were Stanton T. Lawrence, III, Paul J. Zegger, and Carl P. Bretscher, Pennie & Edmonds LLP, of Washington, DC.

JUDGES: Before MAYER, Chief Judge, MICHEL and GAJARSA, Circuit Judges. Opinion for the court filed by Circuit Judge Gajarsa. Chief Judge Mayer dissents.

OPINIONBY: GAJARSA

OPINION: [*1351] GAJARSA, Circuit Judge.

Cadus Pharmaceutical Corporation ("Cadus") appeals the judgment of the United States District Court for the Southern District of California entered after a jury verdict finding the patent claims at issue infringed and not invalid, and assessing damages of $18 million. Because we determine that the asserted claims are obvious as a matter of law, we reverse.

BACKGROUND

The identification [**2] of compounds that bind with particular cell surface proteins is useful in the search for new drugs. When such binding occurs, a cascade of biochemical events is activated within the cell in which a linkage, known as a signal transduction pathway, is formed between the cell surface protein and a gene in the cell's DNA. This linkage allows the cell to respond to signals from the external environment, which is critical for the cell to properly function. Compounds that activate this linkage often prove useful in pharmaceutical applications because many diseases stem from the malfunctioning of cellular communications. [*1352]

In general, when a compound activates a signal transduction pathway, the cell responds by directing the production or non-production of a protein from a responsive gene in the DNA. Protein production involves two distinct processes—transcription and translation. Transcription refers to the process by which a strand of messenger RNA ("mRNA") is created by the expression of a gene. Translation refers to the process by which a corresponding protein (i.e., a sequence of amino acids) is created from the mRNA. Compounds that trigger or enhance transcription and translation are [**3] referred to as agonists, and compounds that block or decrease such activity are called antagonists. The displaying of agonist and antagonist activity is an indication that a compound has bound with the cell surface protein and has activated the signal transduction pathway.

SIBIA Neurosciences, Inc. ("SIBIA") is the owner of U.S. Patent No. *5,401,629* ("the *'629* patent"), which is directed to a cell-based screening method useful for the identification of compounds that exhibit agonist and antagonist activity with respect to particular cell surface proteins. According to the patent, the claimed methods are particularly effective because they allow a scientist to rapidly and reliably screen large numbers of compounds for agonist and antagonist activity. See *'629* patent, col. 1, ll. 45-50. Thus, the scientist could quickly develop a list of candidate compounds that merit further in-depth studies for therapeutic applications. See id. Claim 1, the only independent claim, reads as follows:

> 1. A method for identifying compounds that modulate cell surface protein-mediated activity by detecting intracellular transduction of a signal generated upon interaction of the compound [**4] with the cell surface protein, comprising:
>
> comparing the amount of transcription of a reporter gene or the amount of reporter gene product expressed in a first recombinant cell in the presence of the compound with the amount of transcription or product in the absence of the compound, or with the amount of transcription or product in a second recombinant cell; and
>
> selecting compounds that change the amount of transcription of a reporter gene or the amount of reporter gene product expressed in the first recombinant cell in the presence of the compound compared to the amount of transcription or product in the absence of the compound, or compared to the amount of transcription or product in the second recombinant cell, wherein:
>
> the cell surface protein is a surface receptor or ion channel;
>
> the first recombinant cell contains a reporter gene construct and expresses the cell surface protein;
>
> the second recombinant cell is identical to the first recombinant cell, except that it does not express the cell surface protein; and
>
> the reporter gene construct contains:
>
> (a) a transcriptional control element that is responsive to the intracellular signal that is generated by the interaction [**5] of an agonist with the cell surface protein; and

(b) a reporter gene that encodes a detectable transcriptional or translational product and that is in operative association with the transcriptional control element.

See id., col. 13, l. 44 - col. 14, l. 12.

The methods claimed in the *'629* patent utilize a recombinant cell that is exposed to various compounds in order to determine whether those compounds exhibit the desired activity. This recombinant cell, in addition to the host cell itself, has two basic components: a heterologous n1 cell surface protein and a reporter gene construct. The cell surface protein can be either an ion channel or a cell surface receptor. Ion channels are proteins that act as pores in the cell membrane and allow small inorganic ions to flow in or out [*1353] of the cell. These ion channels open and close based on interaction with certain external compounds. Cell surface receptors, on the other hand, are proteins that span the external membrane of the cell and bind with particular molecules to commence a chain of intracellular reactions that transmit external signals to the DNA. As described above, cell surface proteins are physiologically important [**6] because they play a vital role in the stimulation of signal transduction pathways, and thus, the cell's ability to respond appropriately to stimuli from the external environment.

n1 A cell surface protein is "heterologous" if it is not naturally occurring in the cell.

The second major component of the cell utilized in the *'629* patent is the reporter gene construct, which consists of a transcriptional control element and a reporter gene. The transcriptional control element is a gene that reacts to the signal from the cell surface protein and regulates transcription of the reporter gene. The reporter gene, through the processes of transcription and translation, creates a corresponding protein, referred to as "reporter gene product." Both transcription of the reporter gene and translation to the reporter gene product can be measured.

In the claimed methods, this recombinant cell is used in a battery of assays, the goal of which is to determine if a given compound exhibits the desired binding activity with respect [**7] to a particular cell surface protein. The method of claim 1 contains two assays. In the first assay, referred to as the "compound/no compound assay," the recombinant cell is exposed to a test compound. The amount of reporter gene transcription, or reporter gene product expressed in that recombinant cell, is then compared to the amount of reporter gene transcription or reporter gene product expressed in a recombinant cell that was not exposed to the test compound. In the second assay, known as the "receptor/no receptor assay," two recombinant cells are exposed to a test compound. However, one of the recombinant cells has a cell surface protein, but the other does not. The amount of reporter gene transcription or reporter gene product expressed in both of these cells is then compared. Based on these measurements, the scientist is able to detect whether the compound has bound to the cell surface protein and modulated the signal transduction pathway. This, in turn, allows the scientist to determine whether the compound is a candidate for further study, or should be excluded from consideration.

SIBIA sued Cadus for infringement of the *'629* patent. The court held a Markman hearing, [**8] see *Markman v. Westview Instruments, Inc., 52 F.3d 967, 979, 34 U.S.P.Q.2D (BNA) 1321, 1329 (Fed. Cir. 1995)* (en banc), aff'd, *517 U.S. 370, 134 L. Ed. 2d 577, 116 S. Ct. 1384 (1996),* and issued an order construing numerous claim terms, including "identifying compounds," "cell," "recombinant cell," "comparing the amount," "identical" and "selecting compounds." Only the construction of "cell," "identifying compounds," and "selecting compounds" are relevant to this appeal. Before the district court, Cadus argued that because the claims use the term "cell" without modification, this term should refer to all cells, eukaryotic as well as prokaryotic. n2 Alternatively, Cadus argued that if "cell" should be limited to less than all cells, it should be limited to only mammalian cells, because the examples found in the written description of the patent only discuss mammalian cells. The court decided, however, that because the patentee describes the cells used in the claimed methods as "eukaryotic cells" in the written description, see *'629* patent, col. 3, ll. 52-56, col. 4, ll. 9-11, a person of ordinary skill in the art would interpret cell as found in the claim [**9] language to mean only eukaryotic cells.

n2 Eukaryotic cells, such as animal, plant, yeast, and fungal cells, have nuclei where the cell's genetic material is contained. Prokaryotic cells, such as bacteria and blue-green algae cells, do not have nuclei.

Also important to this appeal is the court's construction of the phrases "identifying compounds" and "selecting compounds." [*1354] At the Markman hearing, the parties disagreed as to whether this claim language required the compounds to be unknown to interact with the particular cell surface protein prior to conducting the assays, or whether these terms include both com-

pounds known and unknown to interact with the cell surface proteins. The court held that the ordinary meaning of "identifying compounds" is determining which compounds interact with a particular cell surface protein from a group of compounds with unknown properties. Thus, the testing of compounds that are known to interact with a particular cell surface protein does not fall within the ambit of "identifying [**10] compounds." Similarly, the court held that "selecting compounds" referred only to choosing compounds from a group previously unknown to interact with a cell surface protein based on the results of the reporter gene transcription and translation analyses.

The case then proceeded to a jury trial. At trial, Cadus asserted that the claims of the *'629* patent were invalid as obvious under *35 U.S.C. § 103*(a) or as not enabled under § 112, P 1. With regard to obviousness, Cadus asserted that the claims of the *'629* patent would have been obvious in view of Deborah J. Stumpo et al., Identification of c-fos Sequences Involved in Induction by Insulin and Phorbol Esters, 263 J. Biological Chem. 1611 (Feb. 1988) ("Stumpo") alone, given the knowledge in the art as embodied in the review article by Henry A. Lester, Heterologous Expression of Excitability Proteins: Route to More Specific Drugs?, 241 Science 1057 (Aug. 1988) ("Lester"). Additionally, Cadus asserted that the claims would have been obvious in view of Stumpo in combination with William S. Chen et al., Requirement for intrinsic protein tyrosine kinase in the immediate and late action of the EGF receptor, [**11] 328 Nature 820 (Aug. 1987) ("Chen"), and Ronald Mark Evans et al., Hormone Receptor Compositions and Methods, WO 88/03168 (May 1988) ("Evans"). With regard to non-enablement, Cadus claimed that if "cell" is to be interpreted to broadly include all eukaryotic cells, the claims are not enabled because the written description discloses only how to practice the invention using mammalian cells. The jury returned a verdict in favor of SIBIA, finding that Cadus infringed claims 1, 2, 4-7, 9, 10, 12, and 14 of the *'629* patent. The jury rejected Cadus's invalidity defenses of obviousness and non-enablement. Damages, based on the calculation of a "reasonable royalty," were assessed at $18 million. Cadus filed numerous post-trial motions, including motions for judgment as a matter of law ("JMOL") or a new trial on the issues of infringement and invalidity, and motions for remittitur or a new trial for damages. All of Cadus's motions were denied. This appeal followed.

DISCUSSION

A. Standard of Review

[HN1] We review the denial of a motion for JMOL following a jury verdict by reapplying the district court's standard of review. See *Tec Air, Inc. v. Denso Mfg., 192 F.3d 1353, 1357, 52 U.S.P.Q.2D (BNA) 1294, 1296 (Fed. Cir. 1999)*. [**12] Thus, we review issues of law de novo. With regard to factual findings, we must presume that the jury resolved all factual disputes in favor of the prevailing party, and we must leave those findings undisturbed as long as they are supported by substantial evidence. See *Jurgens v. McKasy, 927 F.2d 1552, 1557, 18 U.S.P.Q.2D (BNA) 1031, 1035 (Fed. Cir. 1991)*.

[HN2] A factual finding is supported by substantial evidence if a reasonable jury could have found in favor of the prevailing party in light of the evidence presented at trial. See *Tec Air, 192 F.3d at 1358, 52 U.S.P.Q.2D (BNA) at 1296;* see also *Consolidated Edison Co. v. NLRB, 305 U.S. 197, 229, 83 L. Ed. 126, 59 S. Ct. 206 (1938)* ("Substantial evidence is more than a mere scintilla. It means such relevant evidence as a reasonable mind might accept as adequate to support a conclusion."). Thus, substantial evidence review involves an examination of the record as a whole, taking into consideration [*1355] evidence that both justifies and detracts from the decision of the fact-finder. See *In re Gartside, 203 F.3d 1305, 1312, 53 U.S.P.Q.2D (BNA) 1769, 1773 (Fed. Cir. 2000); National Presto Indus., Inc. v. West Bend Co., 76 F.3d 1185, 1192, 37 U.S.P.Q.2D (BNA) 1685, 1690 (Fed. Cir. 1996)* [**13] (holding that a jury verdict must be sustained if it is supported by substantial evidence based on a review of the entirety of the record). [HN3] In reviewing the record, we must draw all reasonable inferences in favor of the prevailing party, and not make credibility determinations or substitute our view of the conflicting evidence for that of the jury. See *Connell v. Sears, Roebuck & Co., 722 F.2d 1542, 1546, 220 U.S.P.Q. (BNA) 193, 197 (Fed. Cir. 1983)*. If, however, after reviewing all of the evidence in a light most favorable to the prevailing party, this court is convinced that a reasonable jury could not have found in that party's favor, we must reverse the denial of JMOL.

B. Obviousness

[HN4] The first step in any invalidity analysis is claim construction, an issue of law that this court reviews de novo. See *Cybor Corp. v. FAS Techs., Inc., 138 F.3d 1448, 1456, 46 U.S.P.Q.2D (BNA) 1169, 1174 (Fed. Cir. 1998)* (en banc). In this appeal, the key issues of claim construction are largely undisputed. As described in more detail above, the method of claim 1 utilizes a recombinant cell having both a heterologous cell surface protein and a reporter gene construct. This cell is [**14] used in two assays—the compound/no compound assay and the receptor/no receptor assay—in which compounds are "identified" and "selected."

Neither party disputes that the terms "identifying compounds" and "selecting compounds" limit the claimed method to identifying and selecting compounds that are not previously known to interact with a particular cell surface protein. The only remaining claim construction issue on appeal is the proper interpretation of the term "cell." According to Cadus, the court erred by limiting "cell" to only eukaryotic cells, as opposed to all cells, both eukaryotic and prokaryotic. SIBIA defends the district court's interpretation by pointing to certain passages in the written description that, it asserts, support the district court's narrower claim construction. See *Comark Communications, Inc. v. Harris Corp., 156 F.3d 1182, 1186, 48 U.S.P.Q.2D (BNA) 1001, 1005 (Fed. Cir. 1998)* (discussing the "fine line" between reading a claim in light of the written description and reading a limitation into the claim from the written description). However, because we decide that the claim is obvious even under the district court's narrow construction of the term [**15] "cell," we need not decide whether the court erroneously imported the "eukaryotic" limitation into the claim, or simply interpreted the claim in light of the specification. Thus, we can proceed to the question of obviousness accepting the district court's construction of claim 1.

[HN5] A patent claim is invalid "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." *35 U.S.C. § 103*(a) (1994). [HN6] While the ultimate conclusion of obviousness is for the court to decide as a matter of law, several factual inquiries underlie this determination. See *Graham v. John Deere Co., 383 U.S. 1, 17-18, 15 L. Ed. 2d 545, 86 S. Ct. 684 (1966)*. These inquiries include the scope and content of the prior art, the level of ordinary skill in the field of the invention, the differences between the claimed invention and the prior art, and any objective evidence of non-obviousness such as long-felt need, and commercial success. See id. [HN7] Because an issued patent is presumed valid, there must be [**16] clear and convincing evidence supporting the obviousness determination. See *Kahn v. General Motors Corp., 135 F.3d 1472, 1480, 45 U.S.P.Q.2D (BNA) 1608, 1614 (Fed. Cir. 1998)*. While the presentation at trial of a reference that was not before the examiner does not change the presumption of validity, the alleged infringer's burden [*1356] may be more easily carried because of this additional reference. See *Applied Materials, Inc. v. Advanced Semiconductor Materials Am., Inc., 98 F.3d 1563, 1569, 40 U.S.P.Q.2D (BNA) 1481, 1485 (Fed. Cir. 1996)*.

On appeal, Cadus argues that the Stumpo reference alone, which was not before the PTO examiner, is sufficient to invalidate the patent under § 103, given the level of skill in the art at the time of the invention. [HN8] In appropriate circumstances, a single prior art reference can render a claim obvious. See, e.g., *B.F. Goodrich Co. v. Aircraft Braking Sys. Corp., 72 F.3d 1577, 1582, 37 U.S.P.Q.2D (BNA) 1314, 1318 (Fed. Cir. 1996); In re O'Farrell, 853 F.2d 894, 902, 7 U.S.P.Q.2D (BNA) 1673, 1680 (Fed. Cir. 1988)*. However, there must be a showing of a suggestion or motivation to modify the teachings of that reference to the claimed [**17] invention in order to support the obviousness conclusion. See *B.F. Goodrich, 72 F.3d at 1582, 37 U.S.P.Q.2D (BNA) at 1318*. This suggestion or motivation may be derived from the prior art reference itself, see *O'Farrell, 853 F.2d at 902, 7 U.S.P.Q.2D (BNA) at 1680*, from the knowledge of one of ordinary skill in the art, or from the nature of the problem to be solved. See *Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 U.S.P.Q.2D (BNA) 1626, 1630 (Fed. Cir. 1996)*; see also *Motorola, Inc. v. Interdigital Tech. Corp., 121 F.3d 1461, 1472, 43 U.S.P.Q.2D (BNA) 1481, 1489 (Fed. Cir. 1997)* ("The suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art."). [HN9] Determining whether there is a suggestion or motivation to modify a prior art reference is one aspect of determining the scope and content of the prior art, a fact question subsidiary to the ultimate conclusion of obviousness. See *Tec-Air, Inc., 192 F.3d at 1359, 52 U.S.P.Q.2D (BNA) at 1298* (stating that the factual underpinnings of obviousness include whether a reference provides a motivation to combine its teachings with another). [**18] Because the jury returned a verdict in favor of SIBIA, we must presume that all factual disputes, such as the motivation to modify, were resolved in its favor. See *Jurgens, 927 F.2d at 1557, 18 U.S.P.Q.2D (BNA) at 1035*.

The parties are in general agreement regarding the teachings of the Stumpo paper itself. Stumpo describes recombinant cells engineered to have both a heterologous cell surface receptor and a responsive reporter gene construct. These cells are identical to the recombinant cells used in the claimed methods. Stumpo describes using these cells in a transcription-based assay in order to detect cell surface receptor activation. According to the unrebutted testimony of Dr. Struhl, the Stumpo paper described a "straightforward functional assay" for analyzing the response of a particular cell surface protein in the presence of a compound. However, these transcription-based assays use the compound insulin, which was known to interact with the surface receptors of Stumpo's recombinant cells. The purpose of these assays was not drug screening, but the characterization of certain as-

pects of the genetic material of the recombinant cell. Claim 1 of the *'629* patent, on the [**19] other hand, claims a method using recombinant cells identical to Stumpo's in transcription-based assays with compounds not previously known to interact with the cell surface protein of the recombinant cell. The only difference between the experiments described in the Stumpo paper and claim 1 is that in the Stumpo paper, the compounds are known to interact with the cell surface proteins, while in claim 1, they are not. Thus, we must presume that the jury determined that there was no motivation to modify the Stumpo reference such that the cells described therein would be utilized with compounds that were not previously known to interact with the cell surface proteins. See id. We hold that this key factual finding is not supported by substantial evidence.

As discussed above, the motivation to modify a reference can come from the knowledge of those skilled in the art, from the prior art reference itself, or from the nature of the problem to be solved. See *In re Rouffet, 149 F.3d 1350, 1358, 47* [*1357] *U.S.P.Q.2D (BNA) 1453, 1458 (Fed. Cir. 1998)*. The undisputed evidence indicates that there was a motivation to modify Stumpo. It was known in the art at the time of the invention that [**20] cells with heterologous cell surface proteins were ideal candidates for drug screening methods. The Lester review article describes the widespread use of such cells in the identification of new drugs:

> A new approach for a systematic program to develop more specific drugs has simultaneously occurred to several investigators. This approach is based on the expression of excitability molecules n3 from DNA clones in cells that readily support such expression and can readily be studied with the full range of modern physiological and pharmacological techniques.

Lester, 241 Science at 1058. Lester goes on to describe that drug screening methods utilizing the expression of excitability molecules (i.e., cell surface receptors) can overcome the "highly empirical approach to the design of drugs" and the lack of functional assays for determining which compounds act on which cell surface receptors. Id. at 1062. These are the identical problems that were being addressed by the *'629* patent. See *'629* patent, col. 1, ll. 36-44 ("The availability of rapid, effective means to identify compounds which interact with . . . cell surface-localized receptors would enable the rapid screening [**21] of a large number of compounds to identify those candidates suitable for further in-depth studies of therapeutic applications."). Similarly, the prior art Dull patent (U.S. Patent No. *4,859,609*) teaches a drug screening method using cells that had a cell surface receptor. Thus, the express teaching in the prior art was that cells having heterologous cell surface proteins, a characteristic found in the Stumpo cells, have been successfully used in drug screening methods and were, in fact, ideal candidates for such use. Additionally, the undisputed testimony was that Stumpo provided a "straightforward functional assay" for determining the response of the heterologous cell surface protein when exposed to a compound. Given that the nature of the problem was the development of rapid and effective drug screening methods based on the response of a heterologous cell surface protein, these teachings provide the motivation to modify Stumpo.

> n3 The "excitability molecules" referred to in Lester are identical to the "cell surface proteins" referred to in the *'629* patent.

[**22]

In response to these teachings, SIBIA merely points out that the cells described in the Lester article and the Dull patent are not described as having reporter gene constructs like those used in the *'629* patent and found in the Stumpo cells. SIBIA, however, is confusing obviousness with anticipation. It is true that these references do not contain an express teaching to use a cell identical to that taught by Stumpo in a drug screening method. It is equally true that these references, particularly Lester, teach that cells with heterologous cell surface receptors were known in the art to have been successfully used in drug screening methods and that the Stumpo cells have such heterologous cell surface receptors. SIBIA's response, that Lester does not mention cells that contain a reporter gene construct in addition to the heterologous cell surface receptor, is to no avail absent some evidence that this additional characteristic would have made such a cell a less attractive candidate for drug screening methods. See *In re Gurley, 27 F.3d 551, 553, 31 U.S.P.Q.2D (BNA) 1130, 1131 (Fed. Cir. 1994)* ("[A] reference will teach away if it suggests that the line of development flowing [**23] from the reference's disclosures is unlikely to be productive of the result sought by the applicant."). SIBIA makes no allegation of a teaching away in Lester. To the contrary, the evidence is unrebutted that cells with reporter gene constructs were also known in the art to be useful in drug screening methods. See U.S. Patent No. *5,091,518* to Sucov. n4 [*1358] Thus, these undisputed teachings in the prior art, "as filtered through the knowledge of one skilled in the art," *Motorola, 121 F.3d at 1472, 43 U.S.P.Q.2D (BNA) at 1489*, as well as the nature of the problem to be solved, provide a sugges-

tion and motivation to use the Stumpo cells, which have heterologous cell surface receptors, in drug screening methods.

n4 Contrary to the suggestion in the dissenting opinion, Sucov is not being "combined" with Stumpo or Lester to achieve the obviousness conclusion. Rather, Sucov is merely cited as an example showing that the use of cells with reporter gene constructs was known in the art to be useful in drug screening methods.

----------End Footnotes----------

[**24]

SIBIA asserts that, regardless of these express teachings supporting the suggestion to modify Stumpo, various trial testimony provides the substantial evidence on which the jury's implied finding of no motivation to modify can be supported. SIBIA relies heavily on the testimony of Drs. Wall, Struhl, and Blackshear. Dr. Wall testified that the Stumpo paper contained no mention of drug screening, and that the experiments described in that paper were directed to the characterization of the fos gene, not to a drug screening method. Wall also testified that the Stumpo paper would not immediately lead one to "conduct drug screening." Similarly, Dr. Struhl testified that there was no indication that the researchers involved in the experiments described in Stumpo used the cells for drug screening. However, simply pointing out that the Stumpo reference itself does not teach the modification is not substantial evidence of no motivation to modify, given the express teaching of the prior art. SIBIA's reliance on the testimony of Wall and Struhl ignores the possibility that the motivation to modify Stumpo can be found outside the reference itself. See id. Thus, while Stumpo does not expressly [**25] suggest that the cells described therein could be used in drug screening methods, the knowledge of those skilled in the art, in particular as embodied in the Lester review article, suggests this modification. SIBIA also points to the testimony of Dr. Blackshear, the senior author of Stumpo, who testified that the Stumpo paper does not contain any reference to drug screening, and at the time those experiments were conducted, "drug screening was not on our minds." However, this testimony, in itself, does not provide substantial evidence in support of the jury's finding. At the time of these experiments, Blackshear was focused on the problem of determining the "fundamental biochemical mechanisms by which insulin worked." Blackshear's personal efforts were limited to a problem different than that addressed by the *'629* patent. Thus, the testimony that he was not thinking about drug screening is irrelevant to the fundamental issue of whether the hypothetical person of ordinary skill in the art, when confronted with the problem of developing drug screening methods, would have been motivated to use the Stumpo cells in such methods. See *Pro-Mold & Tool Co., 75 F.3d at 1573, 37 U.S.P.Q.2D (BNA) at 1630* [**26] (discussing the importance of considering the problem to be solved in the obviousness determination); see also *In re Rinehart, 531 F.2d 1048, 1054, 189 U.S.P.Q. (BNA) 143, 149 (CCPA 1976)* (same).

Finally, SIBIA points to secondary considerations in support of the jury's verdict. In particular, SIBIA points to three licenses or sub-licenses of the *'629* patent, all of which were part of larger licensing packages. However, the mere existence of these licenses is insufficient to overcome the conclusion of obviousness, as based on the express teachings in the prior art that would have motivated one of ordinary skill to modify Stumpo's cells to be used with unknown compounds. See *Newell Cos. v. Kenney Mfg. Co., 864 F.2d 757, 769, 9 U.S.P.Q.2D (BNA) 1417, 1426 (Fed. Cir. 1988)* (holding that [HN10] because the record established such a strong case of obviousness based on the teachings of the prior art, the fact that the product was successful does not overcome the conclusion of obviousness). Moreover, SIBIA has failed to point to any evidence establishing a nexus between the licensing activity and the merits of the claimed screening method. See [*1359] *In re GPAC Inc., 57 F.3d 1573, 1580, 35 U.S.P.Q.2D (BNA) 1116, 1121 (Fed. Cir. 1995)* [**27] ("[HN11] For objective evidence to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention."). Thus, SIBIA's reliance on secondary considerations in support of the jury verdict must fail.

In sum, the undisputed teaching of the Stumpo paper leads one to within a hairsbreadth of anticipation of claim 1 of the *'629* patent. The express teachings in the art provide the motivation and suggestion to modify Stumpo such that the recombinant cells described therein should be used with compounds not previously known to interact with them for purposes of drug screening. SIBIA, the jury verdict winner, has failed to point to any substantial evidence to refute these express teachings, even under the deferential standard with which this court reviews jury verdicts. Thus, claim 1 must be invalidated on the basis of obviousness.

C. Dependent Claims

In addition to finding claim 1 infringed and not invalid, the jury found dependent claims 2, 4–7, 9, 10, 12,

and 14 infringed and not invalid as well. However, in this appeal, SIBIA has failed to argue the validity of the dependent claims separately from the validity of claim 1. Thus, [**28] these claims do not stand on their own, and given our determination that claim 1 is invalid, the remaining dependent claims must fall as well. See *Mehl/Biophile Int'l Corp. v. Milgraum, 192 F.3d 1362, 1367, 52 U.S.P.Q.2D (BNA) 1303, 1307 (Fed. Cir. 1999); Gardner v. Tec Sys. Inc., 725 F.2d 1338, 1350, 220 U.S.P.Q. (BNA) 777, 786 (Fed. Cir. 1984)* (en banc) (holding that [HN12] dependent claims fall with the independent claim on which they depend unless argued separately).

CONCLUSION

We conclude that the implicit finding by the jury that there was no suggestion or motivation to modify the Stumpo reference is unsupported by substantial evidence and the asserted claims are obvious as a matter of law. Therefore, the district court's denial of the Cadus's motion for JMOL on the issue of invalidity must be

REVERSED.

COSTS

Each party shall bear its own costs.

DISSENTBY: MAYER

DISSENT: MAYER, Chief Judge, dissenting.

Today, the court overrides a jury verdict of infringement based on a tenuous obviousness analysis. It recognizes that the Stumpo paper only refers to the use of known substances and presumes that, to find infringement, the jury must have implicitly found that [**29] there was no motivation in Stumpo to utilize the disclosed cells with compounds not previously known to interact with the cell surface proteins. Based on the state of knowledge in the art that cells with heterologous cell surface proteins were ideal candidates for drug screening methods, the court then concludes that the jury's implicit finding is not supported by substantial evidence.

In reality, the court relies on the combination of Stumpo, Lester, and Sucov to establish that the use of heterologous cells with reporter gene constructs was known in the art to be useful in drug screening methods. Stumpo discloses cells identical to the *'629* patent claims, but does not mention their use to test unknown compounds as possible drugs. Lester describes the utility of heterologous cell surface proteins for drug testing, but does not mention cells with reporter gene constructs, which are central to the method of testing of the *'629* claims. Sucov was not even argued at trial, where Cadus argued that either Stumpo or Chen renders the *'629* patent obvious. This analysis is inconsistent with the court's stated conclusion that the *'629* patent is obvious over the Stumpo reference alone in view [**30] of the prior art as argued by Cadus. It fails to recognize that the *'629* patent includes only method claims; Sibia disclaimed all claims [*1360] to the cells themselves when Stumpo was brought to its attention.

The court is making an end-run around the requirement that there must be a motivation to modify the reference along the path taken by the *'629* patent. See *Kolmes v. World Fibers Corp., 107 F.3d 1534, 1541, 41 U.S.P.Q.2D (BNA) 1829, 1833 (Fed. Cir. 1997)* (Invention was not obvious where there was no suggestion or motivation to modify teaching of reference.). It combines a series of references not specifically argued to the jury to conclude that no reasonable jury could possibly find the absence of motivation in the prior art to modify the Stumpo paper to render the *'629* patent obvious. Without citing any motivation to modify in any of the series of references, the court improperly concludes that it would have been unreasonable for the jury to find as a matter of fact that there was no such motivation. See *Tec Air, Inc. v. Denso Mfg. Michigan, Inc., 192 F.3d 1353, 1359, 52 U.S.P.Q.2D (BNA) 1294, 1297-98 (Fed. Cir. 1999)* (Whether a reference provides a motivation to [**31] combine its teachings with other references is a question of fact underlying the legal determination of nonobviousness that we assume the jury resolved in favor of the verdict winner and leave undisturbed if it is supported by substantial evidence.).

The district court properly rejected Cadus' motion for judgment as a matter of law, holding that there was substantial evidence to support a verdict of nonobviousness because the *'629* patent was a "combination of factors that was not apparent to a person of ordinary skill in the art." The trial court found additional support for the jury's verdict in evidence of secondary considerations of long-felt need and commercial success of the *'629* patent. These are factual underpinnings of the legal conclusion of nonobviousness that the jury presumptively resolved in favor of Sibia because substantial evidence supported them. See *id., 52 U.S.P.Q.2D (BNA) at 1298.*

This court improperly rejects this substantial evidence. It opens the door for accused infringers to string together a series of references, which collectively contain the elements of an apparatus (here, the cell with a heterologous cell surface protein and reporter gene construct) [**32] and various suggestions for the use of those separate references. It then would allow an inference of motivation to modify a single reference to render obvious a method claim for utilizing the appara-

tus. All this is in violation of the well-settled mandate requiring a motivation to alter a single reference or to combine multiple references to render the claims of a patent obvious. See, e.g., *id. at 1359, 52 U.S.P.Q.2D (BNA) at 1298* (motivation to combine multiple references); *B.F. Goodrich v. Aircraft Braking Sys. Corp., 72 F.3d 1577, 1582, 37 U.S.P.Q.2D (BNA) 1314, 1318 (Fed. Cir. 1996)* (motivation to modify a single reference); *Grain Processing Corp. v. American Maize-Products Co., 840 F.2d 902, 907, 5 U.S.P.Q.2D (BNA) 1788, 1792 (Fed. Cir. 1988)* ("Care must be taken to avoid hindsight reconstruction by using 'the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.'") (internal citation omitted); *In re Fine, 837 F.2d 1071, 1075, 5 U.S.P.Q.2D (BNA) 1596, 1600 (Fed. Cir. 1988)* ("One cannot use hindsight reconstruction to pick and choose [**33] among isolated disclosures in the prior art to deprecate the claimed invention."). The court has substituted itself for the jury, reweighed the evidence, and combined references that were not before the jury. I would sustain the jury's verdict.